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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/633,093	08/04/2000	Joel S. Greenberger	07787-004003	2079

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/633,093	GREENBERGER ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

--The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

THE REPLY FILED 28 March 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *28 March 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: *See Continuation Sheet*.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-11 and 21-30*.

Claim(s) withdrawn from consideration: _____.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

Continuation of 2. NOTE: The newly submitted claim 31 presented new limitations that require further search and consideration..

Continuation of 5. does NOT place the application in condition for allowance because:

Claims 1-5, 7-10, 21, 22, 24-26, 29, and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (US 5 399 346, 3-21-1995), taken with Greenberger et al (EP 0 381 490 A2, 8-8-90), and Boswell et al (Exp. Hematol 1983) for reasons of record and the following.

In Paper #14, Applicants argue that the Office has not provide a motivation to combine reference teachings, such as why one of skill in the art would be motivated to particularly choose Anderson et al and combine it with Greenberger et al and Boswell et al knowing that TILs and BMSCs respond differently to cryopreservation.

The arguments have been carefully considered but found not persuasive.

With regard to the assertion that the TILs and BMSCs respond differently to cryopreservation, it is noted that original disclosure of the specification does not teach such a difference, rather, the specification teaches, "This invention relates to sequential methods of expanding and cryopreserving bone marrow stromal cells that are transfected and used for gene therapy" (page 2, lines 28-30). The specification indicates with regard to cryopreservation of marrow cells as a whole that "90% of the cells remain viable when thawed" (paragraph bridging pages 2-3), and citing Boswell et al as support. Boswell et al teach, "it was conclusively demonstrated here that stromal progenitors were successfully cryopreserved and were functional after subsequent explantation in culture" (page 321, right column). Apparently, applicants newly and solely rely on the teaching of a later submitted reference by Zaheer et al to support the current assertion that TILs and BMSCs respond differently to cryopreservation, which contradicts the teaching of the present specification. Further, a closer reading of Zaheer reference would find that Zaheer et al does not particularly cryopreserve the marrow stromal cells, rather, they cryopreserve the entire nucleated cell population (BMMC) freshly isolated from a subject (sections "BMMC preparation" and "Cryopreservation and Thawing" on page 181), wherein only one out of one thousand cells in this cell population is bone marrow stromal cells (according to the teachings of instant specification, page 11, lines 6-10). Therefore, first, Zaheer et al were preserving and discussing a different cell population compared to the disclosure of the instant application, wherein the stromal cells are expanded before preservation. Secondly, the conclusion of Zaheer reference is somewhat speculative and insufficient to support the present assertion because they have not cryopreserved a BMSC population, thus, the conclusion from preserving a different cell population could not be used as the sole support for the instant assertion. Therefore, the original disclosure of the specification is relied upon as the basis for combining references, i.e. 90% of the cells remain viable when thawed, and there is no teaching regarding the differences in sensitivity to cryopreservation between the hematopoietic cells and stromal cells.

With regard to the motivation to combine the references, it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references WOULD HAVE SUGGESTED TO THOSE OF ORDINARY SKILL IN THE ART. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the practice of Anderson et al illustrates the knowledge of skilled in the art and the motivation to cryopreserve un-used, transfected cells, i.e. to reduce repeated procedures for obtaining cells from patients, and to maximize the use of obtained and manipulated cells. Moreover, it is noted that cyropreservation of cells in general is a well-known technique in the art, and widely used in the preservation of all cell types, including hematopoietic stem cells and marrow cells as taught by Boswell et al. The ordinary skilled artisan would have been motivated to modify the claimed invention in cryopreserving of transduced BMSCs or other transduced cell type to avoid repeated painful clinical procedure in obtaining BMSCs. The ordinary skilled artisan would have been sufficiently motivated to do so for any types of primary cells, at any stage of the experimentation, i.e. before or after DNA transfection, such as taught by Anderson et al. Thus, the claimed invention as a whole was prima facie obvious in the absence of evidence to the contrary.

Applicants further argue that the cryopreserving process of the present invention differs from those of the prior art. However, it is noted that instant claims encompassing any method of cryopreservation, including those of Boswell and Zaheer.

Therefore, for reason of record and set forth above, the rejection stands.

Claims 1-10, 21-26, 29, and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (US 5 399 346, 3-21-1995), Greenberger et al (EP 0 381 490 A2, 8-8-90), and Boswell et al (Exp. Hematol 1983), as applied to claims 1-5, 7-10, 21, 22, 24-26, 29, and 30 above, and further in view of Lozier et al (Hum Gene Ther 1994) for the reasons of record and following.

Applicants basically reiterated previous argument that Lozier et al reference provides no basis to overcome the deficiencies of the combined teachings of Anderson et al, Greenberger et al, and Boswell et al, that Lozier et al taught a process comprising the steps of first cryopreserving the BMSCs, then thawing and transducing the cells.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the Loister reference is applied for the teaching of a canine model. Although the more common practice in the art is demonstrated by Loister et al, i.e. transforming the BMSCs after thawing, this could be done in a different way as taught by Anderson et al, as long as the cells are viable, an exogenous gene could be expressed at a appropriate level meeting the claim limitation, regardless whether they are transformed before or after the cryopreservation. Thus, the claimed invention as a whole was prima facie obvious.

Claims 1-5, 7-11, 21, 22, and 24-30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (US 5 399 346, 3-21-1995), Greenberger et al (EP 0 381 490 A2, 8-8-90), and Boswell et al (Exp. Hematol 1983), as applied to claims 1-5 and 7-10 above, and further in view of Lobb et al (Biochem Biophy Res Com, 1991).

Applicants argue that there is nothing in this passage that suggests that Lobb et al. transfected any cell, and that Lobb et al. does not disclose expression of any cell surface molecule and does not provide any information that overcomes the deficiencies in the other publications.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Lobb et al clearly teach that VCAM1 is a cell surface molecule that binds to integrin VLA4 and may help recruit VLA4-expressing leukocytes and eosinophils to inflammatory sites in vivo (1st paragraph, page 1498). Further, the passage indicates that Lobb et al not only contemplated that VCAM1 is a surface molecule and could be used for leukocyte targeting, they in fact have transfected cells with the full-length VCAM previously. The reference illustrated the state of the art and what the skilled artisan knows about VCAM and cell transfection.
Therefore, for reasons of record and those set forth above, the rejection stands.